or during at least one of the first extension or the second extension, wherein said chain-terminating agent is incorporated into said extended nucleic acid, and

A3 Cont.

(g) modifying or removing the chain-terminating agent from the extended nucleic acid, if a further extension is to be performed.

9. (Amended) A method for creating a nucleic acid comprising the steps of:

(a) annealing a defined first primer nucleic acid to at least one first single stranded template nucleic acid,

A4

(b) performing a first extension by extending the first primer nucleic acid employing the first template nucleic acid to form a first extended nucleic acid

(c) denaturing the first extended nucleic acid from the first template nucleic acid,

(d) annealing the first extended nucleic acid to at least a second single stranded template nucleic acid whose sequence is not identical to the first template nucleic acid, and

(e) performing a second extension by extending the extended nucleic acid employing the second template nucleic acid to form a twice extended nucleic acid,

(f) adding at least one chain-terminating agent before or during at least one of the first extension or the second extension, and

(g) modifying or removing the chain-terminating agent from the extended nucleic acid, if a further extension is to be performed.

A5

11. (Amended) The method of claim 9, wherein said chain-terminating agent is incorporated into said first or second extended nucleic acid.

A6

16. (Amended) The method of claim 12, further comprising adding at least one chain-terminating agent present before or during each extension.

A7

19. (Amended) The method of claim 9, wherein said first single stranded template nucleic acid or said second single stranded template nucleic acid vary in size, sequence, resistance to cleavage or resistance to exonuclease degradation.

30. (Amended) The method of claim 9, wherein said defined first primer nucleic acid comprises a sequence designed to anneal to a specific sequence comprising said first or second template nucleic acid.

A8

31. (Amended) The method of claim 9, wherein said defined first primer nucleic acid is resistant to cleavage or exonuclease digestion.

32. (Amended) The method of claim 9, wherein said defined first primer nucleic acid is a plurality of primers.

34. (Amended) The method of claim 9, wherein the first extended nucleic acid comprises the primer nucleic acid.

A9

35. (Amended) The method of claim 9, wherein said first or second extended nucleic acid is a recombinant, mutagenized or chimeric nucleic acid.

A9 cont.

36. (Amended) The method of claim 9, wherein said at least one first single stranded template nucleic acid or said at least one second single stranded template nucleic acid is a plurality of template nucleic acids.

A10

39. (Amended) The method of claim 38, wherein said length-altering agent comprises a nucleotide incorporated into said first or second extended nucleic acid.

53. (Amended) A method for creating a nucleic acid comprising the steps of:

(a) annealing a defined primer nucleic acid to at least one first single stranded template nucleic acid,

(b) performing a first extension by extending the primer nucleic acid employing the first template nucleic acid to form an extended nucleic acid,

(c) denaturing the extended nucleic acid from the first template nucleic acid,

A11

(d) annealing the extended nucleic acid to at least a second single stranded template nucleic acid whose sequence is not identical to the first template nucleic acid,

(e) performing a second extension by extending the extended nucleic acid employing the second template nucleic acid to form a twice extended nucleic acid,

(f) adding at least one length-altering agent before or during at least one of the first extension or the second extension, and

(g) modifying or removing the length-altering agent form the extended nucleic acid, if a further extension is to be performed.

All Cont.

54. (Amended) The method of claim 53, wherein said length-altering agent comprises at least one ribonucleotide incorporated into said first or second extended nucleic acid.

55. (Amended) The method of claim 53, wherein said length-altering agent comprises at least one nucleotide analog incorporated into said first or second extended nucleic acid followed by alkylation of said extended nucleic acid.

II. RESPONSE

A. Status of the Claims

Claims 1-57 were filed with the application. Claims 49-52 have been withdrawn in response to Applicants' election of claims 1-48 and 53-57 in response to a restriction requirement dated June 26, 2002. Claims 1, 9, 11, 16, 19, 30-32, 34-36, 39, and 53-55 are currently amended and claims 8 and 20 have been cancelled. Therefore, claims 1-7, 9-19, 21-48 and 53-57 are pending.

The amendments introduce no new matter. Support for the amendments may be found throughout the specification, and particularly in claim 9 as filed, which recites "at least one first template...." Additional support for the amendments herein may be found at page 30, lines 5-31 disclosing as a preferred embodiment single stranded templates and discussing methods for the provision of single stranded templates. Further support for the amendments herein may be found at page 38, line 28 through page 39, line 7 and in FIG. 1, which disclose a defined initial extension primer. Yet further support for the methods as presently claimed may be found at page 36, lines 24-28, which specifies that in one preferred embodiment randomly generated fragments are not to contribute to the nucleic acids created by the present invention.

The claims marked for amendment are provided in Appendix B to this response. For the Examiner's convenience, a clean copy of the pending claims as they stand amended is provided in Appendix C.

B. The Objection to the Specification is Overcome.

The Action objects to an embedded hyperlink. Applicants have herein amended the text of the specification to remove such hyperlinks. Applicants respectfully submit that the objection to the specification is therefore overcome.

C. The Rejections of Claims 16, 48 and 56 under the Second Paragraph of 35 U.S.C. §112 are overcome.

Claims 16, 48 and 56 are rejected as indefinite under 35 U.S.C. §112, second paragraph. The Action alleges that it is unclear what is meant by having at least one chain-terminating agent present before or during each extension.

Applicants have amended claim 16 to more distinctly and clearly point out the invention. Claim 16 now recites the same limitations as the present, and definite, claim 6. Applicants therefore submit that the rejection of claim 16 under the second paragraph of 35 U.S.C. §112 is overcome.

With respect to the rejection of claims 48 and 56 under the second paragraph of 35 U.S.C. §112, Applicants respectfully traverse. It is well-established law that the requirement that the claims particularly point out and distinctly claim the invention is met when a person experienced in the field of the invention would understand the scope of the subject matter that is patented when the claim is read in conjunction with the rest of the specification and in the light of the knowledge of one of skill in the art. *S3 Inc. v. NVIDIA Corp.*, 259 F.3d 1364, 1367 (Fed. Cir. 2001); *In re Moore*, 439 F.2d 1232, 1235, 169 USPQ 236, 238 (CCPA 1971) ("[T]he definiteness of the language employed must be analyzed--not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art.").

Applicants respectfully submit that the specification as filed teaches those with knowledge in the art the full scope and boundaries of the claims with respect to the term "Maxam and Gilbert treatment." Applicants respectfully draw attention to U.S. Patent. No. 5,064,754 filed November 13, 1987 and issued November 12, 1991 (the '754 patent; provided as Appendix D). Claim 20 of the '754 patent contains the limitations of "depurinating or depyrimidating reactions of Maxam-Gilbert." Applicants further draw attention to the specification of the '754, which recites at line 6, column 2, that "each sample is treated with a chemical that specifically destroys one or two of the four bases in the DNA." And further, at lines 8-13, "The 'nicked' molecules are then treated with piperidine which breaks the DNA backbone at the site where the base has been destroyed. This generates a series of labeled fragments the lengths of which depend on the distance of the destroyed base from the labeled end of the segment." Additionally, Applicants respectfully draw attention to U.S. Patent. No. 5,944,971 filed April 23, 1997 and issued August 31, 1999 (the '971 patent; provided as Appendix E). Claim 10 of the '971 patent contains the limitation "wherein said sequencing reaction is a Maxam-Gilbert sequencing reaction."

At the least, "U.S. patents are considered pertinent evidence of what is likely to be known by persons of ordinary skill in the art." *In re Howarth*, 654 F.2d 103, 107 (CCPA 1981). With respect to the clarity of the term "Maxam and Gilbert treatment" in the present claims, Applicants respectfully submit that, in view of the knowledge available to ordinary artisan, the reactions of the Maxam and Gilbert technique were known to those of skill in the art prior to the filing date of the present application.

Finally, Applicants respectfully note that "the purpose of claims is not to explain the technology or how it works, but to state the legal boundaries of the patent grant." *S3 Inc.* at 1369.

Applicants respectfully point out that the language here rejected suffices to state the legal boundaries of at least two issued U.S. patents. These "claims as granted are accompanied by a presumption of validity based on compliance with, *inter alia*, § 112, ¶ 2." *Id.* at 1367; *Budde v. Harley-Davidson, Inc.*, 250 F.3d 1369, 1376 (Fed. Cir. 2001).

Applicants respectfully submit that the claims read in light of the specification and the knowledge of one of skill in the art are therefore clear and definite. Applicants respectfully request reconsideration and withdrawal of the rejections.

D. The rejection of the claims under 35 U.S.C. §103(a) is overcome.

The Action rejects the claims 1-39, 43-48, 53, and 55-57 as obvious over WO 98/01581 (Recombinant Biocatalysts) in view of Rosenthal (U.S. Pat. No. 6,087,095) and further in view of Laney (U.S. Pat. No. 5,679,512). Applicants respectfully traverse.

The holding in *In re Royka*, 490 F.2d 981 (CCPA 1974) states that *all* of the claim limitations must be taught or suggested by the prior art. Further, the Federal Circuit, in the case of *In re Vaeck,* 20 USPQ 2d 1438 (Fed. Cir. 1991), stated that a further two elements must be established in order to make a *prima facie* case of obviousness:

1) the prior art would have suggested to one of ordinary skill in the art to make the invention as claimed; and

2) the prior art demonstrates a reasonable expectation of success of the invention.

Vaeck also emphasizes that both the suggestion and reasonable expectation of success must be found in the prior art, not in the Appellant's disclosure.

Applicants respectfully submit that the present claims are not obvious under 35 U.S.C. §103(a) because the cited art does not provide all the elements of the claimed invention, does not

provide sufficient motive to combine what elements are allegedly disclosed by the cited art, and furthermore, the cited art teaches away from the present invention.

Applicants have amended claims 1, 9, and 53 to more clearly and distinctly point out the invention. In particular, claims 1, 9, and 53 now recite that the extension of the first single stranded template sequence begins from a defined primer. The specification provides in at least one embodiment that a defined primer is one whose sequence and priming location are known. Specification, page 38, line 28 through page 39, line 7 and in FIG. 1. Extension of a polynucleotide template from such a primer therefore proceeds from a known, and therefore defined location. *Id.* Thus, each extension product using that defined primer and the first template begins at a defined location on the template. (See, for example, FIG. 1 of the specification.)

i. Recombinant Biocatalysts discloses random primed amplification of double stranded templates, not the present invention.

Applicants respectfully point out that the Recombinant Biocatalysts reference discloses only the use of random primers for the initiation of polymerase chain reaction amplification from double stranded templates. See, for example, Recombinant Biocatalysts, "Detailed Description of the Invention" beginning on page 8 and extending to the first paragraph of page 9: "The pooled polynucleotides (or at least one polynucleotide) may be subjected to random at least one of random primer extension reactions, or PCR amplification using random primers to multiply portions of the polynucleotide or polynucleotides" (emphasis added).

The present invention is not directed to the random amplification of a pool of double stranded polynucleotides. In fact, the presently claimed methods are not "amplification" as is understood by the relevant artisan in that no multiplication of products is performed. See claims 1, 9, and 53. The claimed process is linear, in that each single stranded template is used to create

a single extension product, which is then annealed to a second single stranded template for further extension. This process does not result in amplification as contemplated and disclosed by the Recombinant Biocatalysts reference.

Recombinant Biocatalysts does not provide for use of defined primer in a non-amplification (*i.e.* linear) method of making polynucleotides from single stranded template as presently claimed and therefore does not provide all the claimed elements of the invention. Applicants therefore respectfully submit that on this basis alone, no valid *prima facie* case of obviousness has been made. But further, viewed as a whole, the Recombinant Biocatalysts reference provides no evidence that an artisan would be motivated to modify the disclosure of Recombinant Biocatalysts to modify the three crucial elements of their methods (random primers, a pool of double stranded templates, and amplification) to achieve the present invention.

ii. There is no cited motive to combine the elements of Recombinant Biocatalysts and Rosenthal or Laney.

The Action alleges that an ordinary artisan would combine the disclosures of Recombinant Biocatalysts and Rosenthal "in order to have achieved the benefit of providing additional cycles of nucleic acid extension for producing a plurality of polynucleotides that encode a polypeptide of interest." The Action, page 5, lines 1-5. Further, the Action alleges that the artisan would be motivated to further combine Laney with Recombinant Biocatalysts and Rosenthal "in order to have achieved an equally effective benefit of nucleic acid extension." The Action, page 5, last line.

However, no citation to the art is provided that makes either suggestion. Nor is the motive to combine to be found within the skill and knowledge of the ordinary artisan. Indeed, the Action provides no specific factual basis or citation for either alleged motive to combine. Furthermore, the alleged motive to combine Laney with the disclosures of the other cited art

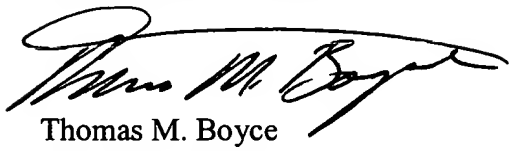
refers to "an equally effective benefit of nucleic acid extension." Yet this statement is devoid of any particular and relevant expected benefit. Respectfully, the only reference to a benefit in the alleged motive to combine Laney is back to the benefits disclosed by the Applicants. This is impermissible hindsight and cannot form a sufficient motive to combine under 35 U.S.C. §103(a).

Nor does the Rosenthal reference provide the necessary motive to combine. Indeed, Rosenthal teaches away from the presently claimed combination. The Rosenthal reference does not provide for the annealing of an extension product made upon a first template to a second template that is not of the identical sequence of the first. The goal and purpose of the Rosenthal methods is to create readable sequence data from a single template. The presence of more than one template wherein the templates are not of identical sequence would only confound the expected results of the Rosenthal methods and therefore Rosenthal can only teach away from the combination as claimed. That a reference teaches away is sufficient on its own to defeat a *prima facie* case of obviousness, even if all the elements of the invention are shown to be available in the art. *Winner Int'l. Royalty Corp. v. Wang*, 202 F.3d 1340, 1349-50 (Fed. Cir. 2000). Therefore, Applicants respectfully request that the rejection be withdrawn.

III. CONCLUSION

In light of the foregoing amendments and remarks, applicants respectfully submit that all claims are in condition for allowance, and an early indication to that effect is earnestly solicited. The Examiner is invited to call the undersigned should the examiner have any questions regarding this response.

Respectfully submitted,



Thomas M. Boyce
Reg. No. 43,508
Attorney for Applicants

FULBRIGHT & JAWORSKI
600 Congress Ave., Suite 2400
Austin, TX 78701
(512) 536-3043
(512) 536-4598 (facsimile)

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